malaria in which the spleen acts as the main point of redistribution of the organisms.

From the results of our studies we venture the following conclusions:

1. Acute splenic enlargement occurs in a large number of cases of early syphilis.
2. This enlargement may be present before the secondary manifestations are apparent, and probably represents the earliest syphilitic visceropathy.
3. The enlargement is either in the form of a soft tumor not unlike that of any other infection or may present itself as a firm, tense tumor.
4. In a small proportion of cases, tenderness, occasionally extreme, may be present.
5. The enlargement is most frequently found in those cases in which the general health has been seriously involved.
6. Acute splenic enlargement in early syphilis tends to disappear under treatment, but may persist and resist treatment longer than any other early manifestation.
7. A striking finding was the frequency with which the splenic enlargement was noted in association with early central nervous manifestations.
8. In no cases in our series was the spleen tumor associated with enlargement of the liver.

CHRONIC LEAD-POISONING IN GUINEA-PIGS: WITH SPECIAL REFERENCE TO NEPHRITIS, CIRRHOSIS, AND POLYSEROSITIS.*

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The experiments recorded in this paper were undertaken primarily with the object of repeating Charcot and Gombault's[7] work on experimental chronic lead nephritis in guinea-pigs. The results of our experiments along these lines are somewhat disappointing, but in the course of the experiments certain interesting changes were obtained in the livers and the serous membranes of the animals experimented upon, which seem to justify more extensive publication.

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* Short notes on this work have appeared in the Proceedings of the Society for Experimental Biology and Medicine, 1912, x, 49-52.

The experiments were performed exclusively upon guinea-pigs, 28 in all. The substance introduced was the same in all cases, carbonate of lead, and it was used in the same way in all experiments, being given by mouth with the food of the animals. As a rule, about ½ grain was given three times a week, but the amount given varied somewhat in different experiments. Since the object of the experiments was to keep the animals under the influence of lead for as long a period as possible, the administration was stopped whenever untoward symptoms developed; that is, whenever the animals began to suffer seriously in their nutrition or when they developed convulsions, which were very commonly observed. On the other hand, many of the animals were given as much lead as they would tolerate, in order to get as definite results as possible.

Since the animals frequently refused their food when lead was added to it, and as they often spilled much of it in the taking, the amount of lead received by each animal cannot be given to a certainty.

All animals eventually died as a result of the continued intoxication, although many of them, except for occasional convulsions, continued in good health and in a good state of nutrition to the last. In fact, some put on an excessive amount of fat, which occurrence in similar experiments has been commented on by other investigators, for instance, by Paviot.[18]

The blood in all cases showed the typical lead anemia. Stippled cells and nucleated erythrocytes were often plentiful in the circulation. Among the latter, megaloblasts were observed frequently. At autopsy the spleen was usually somewhat enlarged; in a few cases considerably so. The venous sinuses were distended and full of erythrophages. The splenic pulp, the marrow, and the liver contained hematogenous pigment in varying amounts. In the marrow the nucleated red cells were extremely numerous and the number of megaloblasts was sometimes very large, more especially so in the long-continued experiments.

The experiments were continued for a much longer time than in any previous series of similar experiments, 13 out of 28 animals surviving for one year or more, 8 of these for two years and more, and 3 even for three years and more. One animal lived almost four years.

THE KIDNEYS. Lead evidently affects the epithelium of the kidneys in a characteristic manner. Its action resembles that of other epithelial poisons, like uranium, chronium, etc., except that it is of a much milder character. The ill effects are almost entirely localized in the distal parts of the convoluted tubules, which have been mistaken for portions of the loops of Henle by some observers. As shown in Fig. 1, the change consists in a granular degeneration of the protoplasm and a pyknotic change in the nuclei. It terminates in necrosis of the cells affected. In few cases the necrosis was preceded by fatty degeneration. Eventually the protoplasm either disintegrates, breaking up into little fragments (Fig. 1), or the cells become detached from the wall of the uriniferous tubules

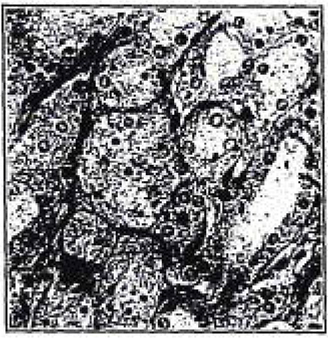

FIG. 1 (× 350).—Granular degeneration of epithelial cells in distal parts of convoluted tubules associated with pyknosis of nuclei and terminating in necrosis. Experiment 4. Guinea-pig 03.

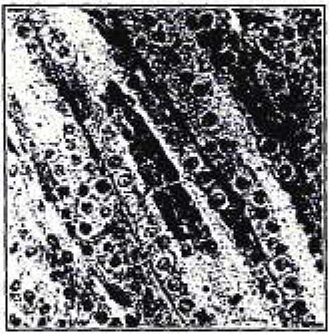

FIG. 2 (× 350).—Epithelial cast in lower part of uriniferous tubule. Experiment 18. Guinea-pig 51.

in toto. In this latter case large epithelial casts may be found in the lower parts of the tubules (Fig. 2). In some cases these are plentiful. Hyaline casts were observed only occasionally. This process seems to continue to practically the same extent throughout the course of the experiments, the destroyed epithelium being constantly regenerated. Mitoses may be found in fair numbers in all specimens, and in the later stages large atypical epithelial cells with giant nuclei (Fig. 3) are often encountered. Regenerated and degenerated cells are frequently seen in the same section of the same tubule. The rest of the tubules are slightly involved, if at all, except in a few cases, where the lesion is more diffuse and involves the more proximal parts of the convoluted tubules.

Examination of the urine at autopsy or during the life of the animals sometimes revealed a slight trace of albumin and commonly degenerated renal epithelium, rarely casts.

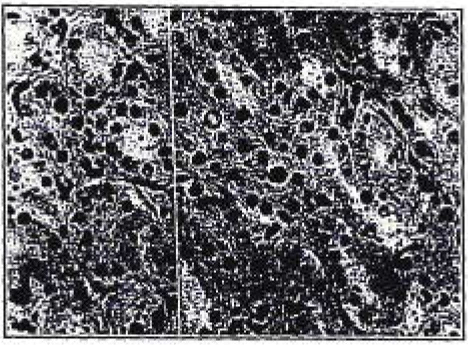

FIG. 3 (× 350).—Giant nuclei in regenerated renal epithelium. Experiment 4. Guinea-pig 03.

Characteristic red blood cells were never found in the tubules, but in some specimens shadows of them seemed to be present in some of the capsules of the glomeruli and in few tubules. In the more acute forms of experimental lead-poisoning, hemoglobinuria associated with hemorrhage seems to be the usual results; but in chronic lead-poisoning one is hardly justified in using the term hemorrhagic nephritis in the way that it is employed by Hoffa.[9]

In the majority of the experiments these were the only lesions found even in animals which had been under the influence of lead for two years and over (see, for example, experiments Nos. 22, 23, and 24), and even in those cases in which small areas of cellular infiltration are noted in the record it is very doubtful whether these can be ascribed to the lead-poisoning, because such lesions are not uncommonly found in the kidneys of untreated apparently normal guinea-pigs.*

This leaves six animals only (Experiments Nos. 11, 12, 16, 18, 25, and 27) that show more definite interstitial changes, and in four of these they are very slight indeed. The kidneys in these four cases did not show any gross lesions, and microscopically a few small areas were encountered in which small groups of tubules (probably adjoining sections through one and the same tubule) were in a state of collapse, and in which the connective-tissue between these tubules was very slightly proliferated. Even in the remaining two animals the condition is by no means striking.

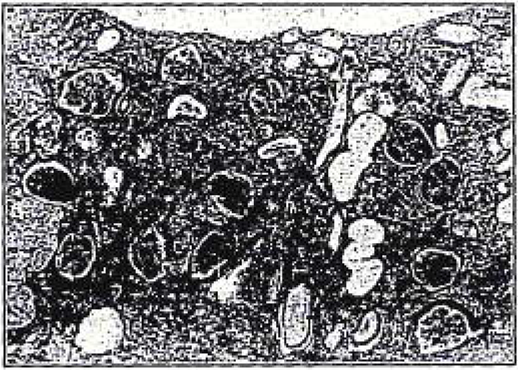

FIG. 4 (× 100).—Area of chronic nephritis with collapse of many tubules, dilatation of others, and capsular thickening of glomeruli. Experiment 27. Guinea-pig 69.

In Experiment 18 it is described as follows: "The kidneys show just visible, fairly regular pitting of the surface," and in Experiment 27, "kidneys fairly large, capsule non-adherent, surface coarsely and finely dimpled."

The most marked lesion found in the latter case[27] is shown in Fig. 4. The photomicrograph gives an idea of the slight depression on the surface, which is largely due to the collapse of the tubules. The slight thickening of the connective-tissue between them is also clearly brought out. At the base of the picture there is a moderate infiltration of the tissues with lymphocytes near some large vessels. The picture also shows a corresponding enlargement of other tubules in the vicinity, which is the usual thing in such cases.

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* See Ophüls. Occurrence of Spontaneous Lesions in Kidneys and Livers of Rabbits and Guinea-pigs, Proc. Soc. Exp. Biol. and Med., 1911, viii, 75.

The epithelium in these dilated tubules is partly atrophied, but in some the epithelial cells are evidently enlarged and proliferated.

The glomeruli in this figure are also of some interest, because they show the only lesion which was ever observed in them, and which occurs practically exclusively and constantly in foci of this character, namely, a fibrous thickening of the capsules which is usually rather moderate in extent and may be associated with a slight proliferation of the capsular epithelium.

None of the specimens show the slightest lesions in the bloodvessels.

The condition even in the most advanced case is in no ways similar to what one finds in the kidneys in human cases of chronic lead-poisoning. In them the involvement of the bloodvessels and of the glomeruli is a striking feature of the process, so much so that to all appearances the vascular lesions are primary, the kidneys in many cases being indistinguishable histogically from other forms of arteriosclerotic nephritis.

In a general way the lesions in the guinea-pig resemble histologically those observed in uranium nephritis in the same animals, although they are by no means so severe nor so extensive.

The reports in literature in regard to the action of lead on the kidneys of animals are very contradictory.* On the one hand we have Charcot and Gombault's[7] well-known report, according to which they found "granular" kidneys in 7 out of 15 guinea-pigs after continued administration of carbonate of lead by mouth. They claim that histologically the alterations found were identical with those in human lead nephritis. Their experiments lasted from two days to one year, and in one instance "distinctly granular" kidneys were found as early as the seventeenth day (Experiment 10). None of the later investigators have been able to repeat these experiments so successfully, if we except a rather general statement by Provost et Binet,[12] who after some rather unsuccessful preliminary attempts used Charcot and Gombault's method of feeding carbonate of lead to guinea-pigs on 25 animals; 17 of these survived the first month, most of them dying between the second and third months, One animal only lived six months. They say "lésions renales très accentuées chez la plupart d'entre eux, surtout quand l'intoxication avait duré longtemps," and make a similar statement in regard to fourteen rats that were treated similarly. It is to be regretted that they do not give their observations in greater detail. The experiment of Paviot[18] with carbonate of lead on six rabbits in which he found no gross lesions, but microscopically what he calls extensive sclerosis in two animals after about six months, are no more convincing, to my mind, especially as such lesions very commonly occur spontaneously in rabbits. What is particularly suggestive in this regard is the fact that the lesions in his cases appear to start in the pyramids and extend into the cortex radially as the spontaneous lesions in rabbits are likely to do.

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* At the end of the paper there is a list of the more important articles in historical sequence.

Coën and d'Ajutolo,[11] who experimented on rabbits with acetate of lead for at most 153 days, found only slight interstitial lesions, but believe that a longer administration of the poison might have produced a true renal cirrhosis, a surmise which hardly seems to be justified in the light of our experience. Jores,[26] who also used rabbits, found one small scar only in a rabbit that had been under experimentation for fourteen months and twenty days. All others who have paid any special attention to this point (Hoffa,[9] Oliver,[13] Stieglitz,[14] Annino,[16] Hirsch[20]) describe lesions no more marked than those which were observed in our own experiments.

The conclusions, therefore, seems to be justified that in the warm-blooded animals so far experimented on (guinea-pigs, rabbits, rats, cats, and dogs), chronic lead-poisoning produces in the kidneys primarily epithelial lesions, which condition eventually may be followed by a certain type of granular atrophy, due to collapse of groups of tubules, associated with some fibrous thickening of the connective-tissue between these tubules and of the capsules of the glomeruli in these areas, but that these changes always remain quite limited and are by no means constant. On the basis of my experiments I do not believe, as Jores[26] does, that these later lesions are at all more common in guinea-pigs than they are in rabbits. Certainly nothing has ever been reproduced in any of the animals mentioned which in any way resembles human lead nephritis, Charcot and Gombault's[7] statements to the contrary notwithstanding.*

The existence of epithelial lesions is acknowledged by all investigators, but even in this regard there are to be found certain minor discrepancies in the various reports concerning the exact form of degeneration of the protoplasm and of the nuclei of the cells involved. Annino[16] claims never to have seen any mitoses, which is certainly quite remarkable.

One curious feature in our experiments is the fact that whereas many of the other investigators have described calcareous deposits in the uriniferous tubules, often in large numbers, we have not encountered them in the kidneys of any of our animals, in spite of the fact that they were looked for carefully. They were first observed by Charcot and Gombault,[7] who say in regard to them, "On the cut surface one finds, especially in the pyramid, a large number of whitish, highly refractile dots and lines made up of solid masses of calcareous material, which infiltrates the tubules," and in another place, "One finds a certain number of the narrow branches of the loops of Henle filled with solid calcareous masses, the cellular structure of which becomes evident after decalcification." They are prominently mentioned and discussed by Prevost and Binet,[12] whereas Stieglitz[14] found them only rarely. Hirsch[20] and Hoddick[27] also mention them, others do not seem to have paid any special attention to this point. Paviot[18] did not find them in his few experiments on rabbits, and believes that Charcot and Gombault's[7] experimental results are largely due to the blocking of the tubules by the calcareous masses. These deposits are of great interest on account of the apparent close relation of chronic lead-poisoning in man to gout. The occurrence of similar calcareous deposits, containing urates also in the pyramids of the kidneys, is very common in such cases in man, and these sometimes are the only manifestation of the existence of a gouty diathesis. Whether the deposits in the animals also contained urates does not seem to have been ascertained. I may state here in passing that in spite of special attention to this point no evidences of gout was ever detected in any of our animals.

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* The statement which is sometimes found in literature that Leyden reported successful experiments of this character is entirely erroneous. In his paper read before the Verein f. innere Medicin at Berlin, March 19, 1883, and published in the Deutsch. med. Woch., 1883, ix, 185, Leyden reports a case of human lead nephritis, but makes no mention of any experiments whatever, nor does his pupil Muschold in his dissertation, Die Bleivergiftung eine Ursache chronischer Nierenerkrankung, Berlin, 1883.

The reports in regard to glomeruli and bloodvessels are also most curiously conflicting, which in itself suggests that they are by no means well marked or constant. A hyaline degeneration of the glomeruli has been described by Coën and d'Ajutolo[11] and by Stieglitz,[14] which we cannot confirm in our specimens. It is often difficult to make out exactly what sort of changes the authors allude to, because their statements are very general and few of them give any illustrations of the lesions encountered; but at best the lesions described appear to be slight, somewhat like those described above in our own specimens (slight fibrous thickening of capsules of Bowman, possibly associated with some atrophy of the glomeruli themselves, and a moderate proliferation of the epithelial lining of the capsules), and they are in no way comparable to the glomerular changes observed in human nephritis, either of the arteriosclerotic type or in well-marked glomerulonephritis.

So far as the bloodvessels are concerned, much emphasis is usually placed in reviews of the literature on Annino's[16] work, probably on account of a notice in the Virchow-Hirsch Jahresberichte (1894, I, 375), stating that he found "severe endarteritis which even lead to complete vascular obstruction." If one reads the original, however, and particularly the description of findings in the individual experiments, one discovers to his surprise that in most organs the arterial lesions were very slight indeed, possibly non-existent, except in the lungs, where Annino actually claims to have seen an endarteritis tending to occlusion.*

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* Annino[16] used 9 animals altogether in his experiments, 2 young dogs, 3 rats, 2 rabbits, and 2 guinea-pigs. The animals were observed for a few months only, one of the dogs lived longest, for seven months. None of them showed any important gross lesions.

Similar conditions in the pulmonary vessels have been noted by Stieglitz,[14] Greven,[25] and Jores,[26] but Jores very correctly pointed out that normally these vessels in rabbits, and he might have added in guinea-pigs, have very thick walls and a very narrow lumen, and that normally also the intima may be somewhat thicker and more cellular in places. Jores[26] still believes that he found a thickening of the intima which exceeded the physiological limits in those of the animals which had been exposed to the influence of lead longest, but even so he believes these slight alterations to be unimportant, and at the end of his paper he emphatically denies the importance of the vascular changes described by the above mentioned authors, and also by Maier and his coworkers. I fully agree with him on this point and wish to state positively that neither in my specimens have I ever seen anything resembling arteriosclerosis, nor am I at all convinced, from a careful study of the literature, that such changes have ever been produced in animals by chronic lead-poisoning.

The heart, so far as its weight is concerned, and the aorta were found to be entirely normal in all my animals.

THE LIVER. The lesions in the liver in chronic experimental lead-poisoning have attracted comparatively little attention, and yet from the results of my experiments it would appear as if they were really more important than those which occur in the kidneys.

Coën and d'Ajutolo[11] seem to have been the first to pay some attention to the liver. They describe primarily a "necrotic, granular degeneration of the liver cells," and later a chronic hyperplastic periangiocholitis. Since the latter, however, is commonly observed spontaneously in rabbits,* which animals they used for their experiments, this latter condition was possibly not the result of the lead-poisoning.

Oliver,[13] who also used rabbits, makes the following statement: "In the liver of animals and in the liver of lead-workers there will be found an atrophied, cloudy, or granular condition of hepatic cells, amounting at times to a true fatty degeneration. The columns of cells become irregular and slender, and thus become separated from each other by spaces of considerable size. For nearly all the specimens taken from human beings and ruminants these spaces between the individual hepatic cells and rows of cells were occupied by small round cells. There was an increase of connective-tissue elements, derived in all probability from the capillaries or the sheath which surrounded them. In other words, there was an intercellular cirrhosis not unlike that met with in congenital syphilis. The capillaries of the lobules were generally found to be overdistended, a condition observed nearer the centre than the periphery. Interstitial inflammation with degeneration of columns of liver cells was so generally present in all specimens that I cannot but regard this as a constant lesion, and as one likely to arise in the early stages of lead-poisoning." In the accompanying plates he shows the microscopic picture of a liver with well-advanced cirrhosis in a girl, aged eighteen years, who had worked only forty days in a lead-factory. His Fig. XXVIII, showing the microscopic picture of the liver of a rabbit with lead-poisoning, does not show any resemblance to the changes observed in our animals.

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* Ophüls, loc. cit.

Laffitte[15] emphasizes the hepatic changes in chronic lead-poisoning more strongly than any other author. He gave carbonate of lead to four rabbits by mouth for from one and one-half to five months and found no epithelial lesions except atrophy, but marked early interstitial lesions resembling those of cirrhosis. He further presents six human cases of cirrhosis in chronic lead-poisoning, two of which are personal observations. What has been said above in regard to spontaneous lesions in rabbits naturally applies here.

Annino[16] also describes degenerative lesions in the liver and some perivascular cellular infiltration and proliferation of the periportal connective-tissue.

Jores[26] found hematogenous pigmentation to a varying degree and marked hyperemia in the liver of his rabbits, but no other important changes.

The following interesting statement is made in Mallory's recent book on *Principles of Pathological Histology*:* "Lead salts given to rabbits and other animals in amounts just below the minimum fatal dose will produce in a few days a hyaline lesion in the liver cells similar in all respects to that found in the alcoholic cirrhosis of man. Some of the cells undergo necrosis and are removed by the digestive action of leukocytes. Regeneration of liver cells is shown by mitotic figures. This observation suggests that the so-called alcoholic cirrhosis of man may possibly be due to lead."

This is by far the most accurate observation so far recorded in literature.

It is astonishing that the severe gross changes in the liver which follow later in the stages of chronic experimental lead-poisoning and which may be well developed at the end of nine months (see our observation to 14) have apparently never been recorded before.

The initial lesion which has been constantly found in all our cases in which a microscopic examination was made is, as Mallory states, a peculiar hyaline degeneration of the protoplasm of the liver cells associated with pyknosis of the nuclei, eventually terminating in necrosis. The change is clearly shown in three cells in the centre of Fig. 5. The degenerated cells occur either singly or in small groups of two to three cells without any characteristic distribution so far as could be made out. Eventually the remnants of the cells are either absorbed or may be removed by leukocytes, as stated by Mallory. New cells to take their place are produced by mitosis.

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* F. B. Mallory, The Principles of Pathological Histology, Philadelphia, 1914, p. 507.

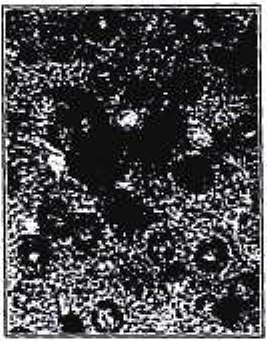

FIG. 5 (× 750).—Hyaline degeneration of small group of liver cells with pyknosis of neuclei. Experiment 3. Guinea-pig 02.

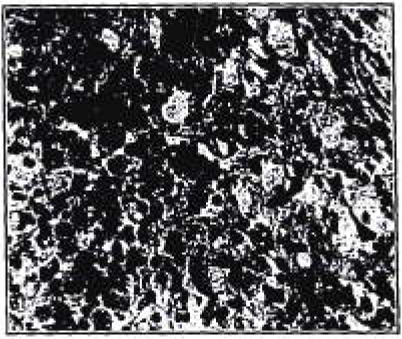

FIG. 6 (× 350).—Fatty degeneration and necrosis of large central group of liver cells with beginning collapse of tissue. Fibrous thickening of capsule. The cells with deeply staining nuclei in centre of field are situated in the central vein of a lobule. Experiment 14. Guinea-pig 3.

In the end these degenerative lesions which may be associated with fatty degeneration may become more and more extensive, so much so as to destroy large parts of the liver tissue, as shown in

Fig. 6, in which practically all the cells in the field are either in a state of severe degeneration or actually necrotic and disintegrating.

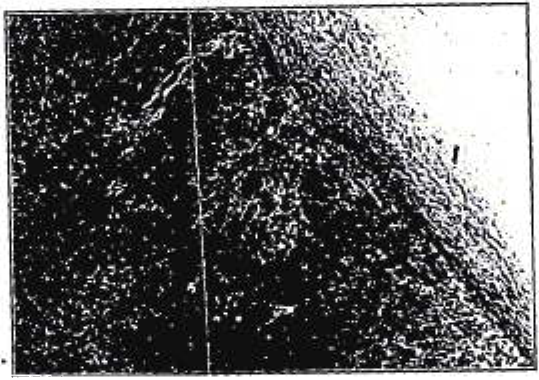

FIG. 7 (× 100).—The same specimen taken with a low power, showing distribution of lesion and marked chronic perihepatitis. Experiment 14. Guinea-pig 3.

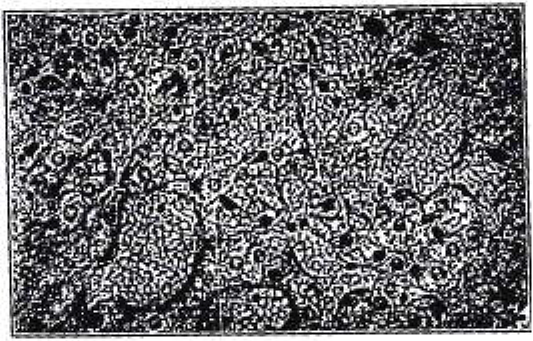

FIG. 8 (× 350).—Dilatation of capillaries due to atrophy and necrosis of liver cells. Experiment 16. Guinea-pig 1.

The removal of the dead liver cells naturally causes a tendency to collapse on the surface, and in the interior of the organ a tendency to dilatation of the capillaries in the same way, as one observed it in the red parts of a human liver in subacute yellow atrophy.

Fig. 7 is a photomicrograph of the same lesion shown in Fig. 6 at a lesser magnification, and brings out more clearly the peculiar localization of it. The dilatation of the capillaries in the interior of the organ is well shown in Fig. 8, whereas the tendency to collapse is clearly observed in Fig. 9, in which there are also some large areas of capillary dilatation.

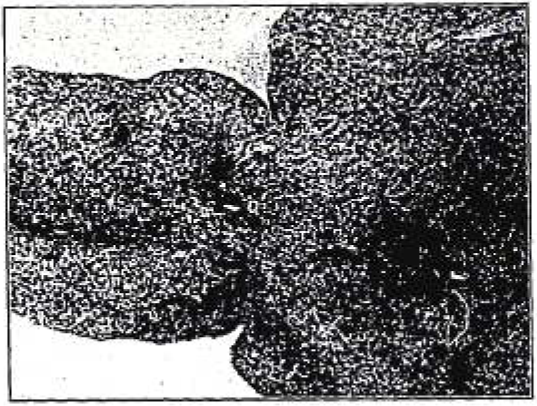

FIG. 9 (× 100).—Extensive areas of degeneration and necrosis of liver cells with dilatation of capillaries and deep retractions due to collapse. Experiment 22. Guinea-pig 33.

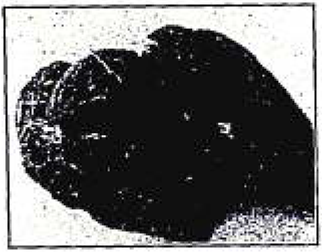

FIG. 10.—Gross appearance of liver of guinea-pig 54 (Experiment 21), showing irregular fibrous thickening of capsule, finely granular surface, and large irregular depressions.

The condition is similar to subacute yellow atrophy. Sometimes it involves the organ diffusely, as in observation No. 14, in which the liver remained fairly smooth; but more commonly it is localized in circumscribed spots, and in this way produces first a more or less regular pitting of the surface. Later there is a markedly granular appearance with shrinkage, which in the gross strongly suggests cirrhosis (Figs. 10 and 11).

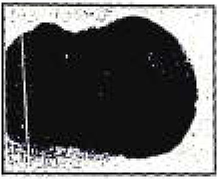

FIG. 11.—Gross appearance of liver of guinea-pig 35 (Experiment 17), showing finely granular surface and dimpling.

There is this important difference, however, that there is little if any proliferation of the connective-tissue associated with the process, at least in guinea-pigs. Fig. 12 is taken from the specimen in which the interstitial lesions were most clearly developed in an animal which had survived for one year and eleven months (observation No. 20). The later animals (Nos. 21, 22, 26), in all of which the hepatic lesions were well developed, showed less proliferation

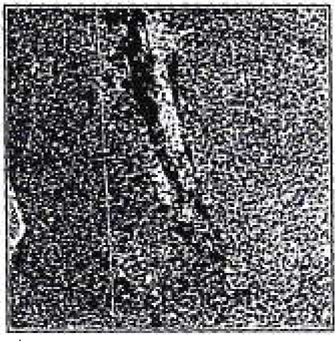

FIG. 12 (× 100).—Cellular infiltration and fibrous thickening of periportal connective tissue. Experiment 20. Guinea-pig 24*a*.

in the periportal connective-tissue, which in observations No. 22 (two years and two months) and No. 26 (three years and one month) amounted to no more than a slight cellular infiltration. It does not appear to be likely, therefore, that the lack of connective-tissue formation was due to insufficient time for its development or that a prolongation of the experiments, if possible, would have brought more striking results in this regard.

Kretz* defines cirrhosis as a "focal recrudescent chronic atrophy modified by intermittent degeneration of the parenchyma." It appears to me that his definition applies much more correctly to the changes observed in these guinea-pigs than to cirrhosis in man, and that it seems evident that such a process cannot in itself explain the abundant connective-tissue formation in human cirrhosis. And yet the process in our experiments would seem to be specially suitable to reproduce conditions resembling human cirrhosis because it is associated with severe anemia, a combination to which Kretz* also alludes in his paper. It is worthy of note that in spite of the constant occurrence of degenerative lesions of moderate degree in the livers of all guinea-pigs examined, and of slight pitting in all animals after the ninth month, severe changes were found to be comparatively rare. They were present in Cases Nos. 14, 16, 17, 20, 21, 22, 26 in seven out of twenty-eight animals. Of the three cases which lasted over three years, one only showed advanced changes in the liver.

The following is a short *resumé* of the more interesting experiments:

14. Guinea-pig 3. The liver is much reduced in size, measuring 5 x 3½ x 2 cm. (normal measurements at least 7 x 4½ x 2½ cm.). The capsule is slightly thickened diffusely, and in places there is a very marked fibrous thickening of the same (Fig. 7). The surface of the liver is smooth, but the shape of the organ is much distorted. The sharp edges are all rounded, and here and there along the anterior now rounded border one sees rather coarse nodules with fairly deep rounded depressions between them. The microscopic appearances of the liver tissue are shown in Figs. 6 and 7. There are many large areas of fatty degeneration and necrosis in which one finds considerable granular hematogenous pigment. The periportal connective-tissue is cellular, slightly increased in amount, and sends slender projections to the thickened capsule. The spleen is large, over twice normal size; marked perisplenitis; few drops of clear fluid in abdomen; chronic pericarditis.

16. Guinea-pig 1. The liver is slightly reduced in size (5½ x 4½ x 2¾ cm.). The capsule is slightly thickened. The surface is finely and evenly granular, showing dark-red spots about 1 mm. in diameter with a grayish depressions between them. On the lower surface

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* Lebercirrhose, Verh. der Deutsch. path. Ges., 1904, viii, 54.

of both lobes there are some deep irregular fissures. Microscopic sections show large areas of fatty degeneration and necrosis with marked dilatation of capillaries (Fig. 8) and areas of collapse on the surface of the liver. No hematogenous pigment was found in the liver. The periportal connective-tissue is slightly thickened and infiltrated with lymphocytes. The spleen was of about normal size. Marked, slightly hemorrhagic, ascites; chronic pericarditis; sero-fibrinous pleurisy.

17. Guinea-pig 35. The liver is of nearly normal size, measuring 7 x 5 x 2½ cm. The surface is distinctly granular (Fig. 11). The granules measure about 1 mm. in diameter. In addition there is some deep pitting, more especially on the lower surface of the liver, where there are many deep fissures. Sections show large areas of fatty degeneration and necrosis, with collapse of tissue on the surface, causing the granular appearance and the pitting. Slight cellular infiltration of the periportal connective-tissue; slight perihepatitis; marked ascites; chronic pericarditis; chronic pleurisy with effusion; anasarca.

20. Guinea-pig 24a. The liver is much shrunken, measuring 5¾ x 4 x 2 cm. The capsule shows a marked irregular fibrous thickening. The shape of the liver is much altered, much like the liver of Guinea-pig 3. The edges are rounded off and the various lobes firmly adherent to one another. The surface shows coarse nodules with deep furrows between them. Sections show large areas of fatty degeneration and necrosis with dilatation of capillaries and collapse of the liver tissue. The periportal connective-tissue is normal except for a slight cellular infiltration. The spleen is large (3½ x 1¾ x ¾ cm.). Marked ascites; hemorrhagic pericarditis; hemorrhagic pleurisy.

21. Guinea-pig 54. The liver is considerably reduced in size, measuring 6 x 4 x 2 cm. The capsule shows a marked irregular fibrous thickening. The surface is uneven and distinctly finely granular, There is also much deep pitting (Fig. 10). Sections show many large central areas of fatty degeneration and necrosis, with collapse of liver tissue and dilatation of capillaries. Much hematogenous pigment is found in the capillary endothelium. In this guinea-pig the cellular infiltration and proliferation of the periportal connective-tissue is more marked than in any of the others as shown in Fig. 12. The spleen is large, 4 x 2½ x 1 cm. Much ascites; hemorrhagic pericarditis; serous pleurisy; anasarca.

22. Guinea-pig 33. The liver is slightly reduced in size, measuring 6½ x 4½ x 2½ cm. The capsule is slightly thickened in a few places. The surface is distinctly granular, the granules measuring about 1 mm. in diameter. There is some deeper pitting on the left side above and below. Sections show fatty degeneration and marked atrophy of the epithelial cells in the centres of the lobules, with dilatation of the capillaries. The granules on the surface are due

to collapse of liver tissue. In the periportal connective-tissue one finds a slight cellular infiltration. The spleen is moderately enlarged, about twice normal size. Little ascites; hemorrhagic pericarditis; serous pleurisy.

26. Guinea-pig 46. The liver is much reduced in size, measuring 6 x 4 x 2 cm. The capsule is much thickened and the upper surface of the liver is attached to the diaphragm. All lobules are adherent to one another and the shape of the organ is much altered, much like the livers of guinea-pigs 3 and 24*a*. The cut surface of the right side shows large areas of necrosis and softening. Microscopic sections show the usual lesions and in addition large bacterial necrosis. The spleen is small, firmly attached to the fundus of the greatly dilated stomach by the thickened capsule. Ascites; hemorrhagic pericarditis; serofibrinous pleurisy.

What makes these changes even more deceptively like human cirrhosis is the constant association in them of severe hepatic disease with accumulations of fluid in the peritoneal cavity and with chronic inflammatory lesions of the serous membranes, more particularly of the peritoneum in the upper part of the peritoneal cavity, which are so commonly observed in human cirrhosis.

The possibility of lead as an etiological factor in human cirrhosis as suggested by Mallory has been discussed by few clinical writers. Aubry reported two cases of Coutenot's in 1865, which in literature are usually recorded twice, both under Aubry and Coutenot's names.[36] In one of these cases a typical cirrhosis was found at autopsy in a girl suffering from chronic lead-poisoning. Laffitte, as stated, has collected six cases of this kind, and Oliver[37] seems to favor the idea that lead is an important factor in certain cases of cirrhosis. Potain[38] also believes that chronic lead-poisoning is definitely though rarely a cause of cirrhosis, and cites some cases in support of his view. He believes that the prognosis of this form is unusually good. It has been suggested that alcoholic beverages are commonly adulterated with lead, still the use of sugar of lead for clearing and sweetening the wines has been long discarded. On the whole there seems to be little clinical evidence so far to connect human cirrhosis with chronic lead-poisoning.

In our service among twenty-five necropsies on painters who had all shown more or less evidence of lead-poisoning, only one case of advanced cirrhosis was observed, and this one in a man who except for some anemia did not show any other evidences of lead-poisoning. In addition there were in this series four cases of slight beginning cirrhosis, which would hardly be suggestive of a more common occurrence of cirrhosis in lead workers. It may be interesting to note here that many of the livers in the more marked cases of chronic lead-poisoning did show some degenerative lesions in the epithelium, resembling those observed in the majority of our guinea-pigs.

As a unique finding in our series of animals, I wish to call attention to the severe myocarditis observed in Case 28 (guinea-pig No. 12), of which photomicrograph 13 gives a representation. This animal happens to be the one longest surviving (for three years and ten months). There were present in addition in this animal marked degenerative and slight interstitial lesions in the kidneys, moderately advanced lesions in the liver, also some ascites, chronic pleurisy with hydrothorax, and a slight chronic pericarditis with effusion. No similar lesions of the heart muscle were discovered in any of the other animals, even in those with much more marked degrees of pericarditis.

THE SEROUS MEMBRANES. The serous membranes have received even less attention than the liver in chronic experimental lead-poisoning. The frequency of pericardial lesions is commented upon by Charcot and Gombault[7] in the following statement: "At autopsy of the animals we were impressed by the condition of the pericardium, which we found diseased in 7 out of 15 cases. There was found in the serous cavity an effusion, sometimes simple, sometimes bloody, associated with the formation of abundant false membranes on the surface of the two layers of the pericardium." Their records of the individual cases show that this condition eventually leads to marked fibrous thickening, more especially of the visceral layer, and sometimes to adhesions. They did not observe any changes in pleura or peritoneum except in Observation 9, in which they note the presence of an enormous "blood-clot in the peritoneum," without further discussion. Prevost and Binet[12] also noticed pericarditis in 8 out of 25 guinea-pigs, which were given carbonate of lead by mouth, like the animals in the experiments

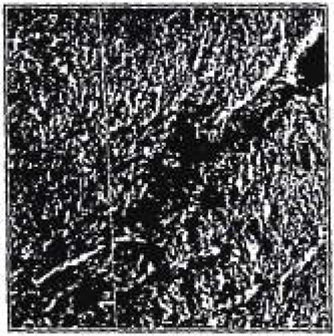

FIG. 13 (× 100).—*Myocarditis.* Experiment 28. Guinea-pig 12.

of Charcot and Gombault.[7] Stieglitz[14] observed pericarditis in two of his animals. Paviot[18] found a localized gelatinous pericarditis in one of his rabbits. This animal also had been given carbonate of lead in large doses. These are the only references to experimental observations of this kind which I have been able to find in literature and they seem to have attracted practically no attention. Our clinical knowledge in regard to this subject is still more rudimentary. Galvagni* seems to be the only one who has discussed the subject at some length. He says: "In the last year I had the opportunity to observe in my clinic at Modena two cases, which induce me to believe that inflammatory lesions in the peritoneum, more especially in the mesentery, may be a possible result of chronic lead-poisoning." One of these cases came to autopsy, and Foà found perisplenitis; perihepatitis, with total adhesion of the stomach, of the liver, and of the spleen to the diaphragm; total sclerosis of the great omentum; chronic sclerotic mesenteritis with retraction of all loops of the bowel; sclerosis of the solar plexus, etc.

The constancy and extent of the lesions in our guinea-pig is certainly remarkable. Even in the more acute form of the intoxication, especially when the animals receive large doses of lead, small, often hemorrhagic, effusions take place into the serous cavities, as is shown in Experiments Nos. 1 to 5 inclusive. The next series of animals that were given much smaller amounts (Nos. 6 to 11) and also cases 12 and 13, in spite of large doses, show normal serous membranes; but from there on, with the one exception of Experiment 18, the animals all have marked lesions in their serous membranes.

14. Guinea-pig 3 had a few drops of clear fluid in the peritoneal cavity. In the upper part of the abdomen the peritoneum is slightly thickened. The thickening is quite diffuse and somewhat varying in intensity. The capsule of the spleen is thick and fibrous. The parietal pericardium is quite thick and white, and there are some white spots on the visceral layer. The pleuræ are moist, otherwise normal. Smears of the serous membranes show many red-blood corpuscles, many of them nucleated, some megaloblasts, few endothelial cells and lymphocytes, few polymorphonuclear leukocytes. No bacteria were found in spite of the use of various staining methods and in spite of careful search.

15. Guinea-pig 2 had a marked ascites, slight chronic perihepatitis, and slight chronic pleurisy.

16. Guinea-pig 1 had a marked, slightly hemorrhagic, ascites. The peritoneum was slightly thickened, smooth, hyperemic. There were old adhesions between spleen and stomach and between liver and kidney. Slight perihepatitis. Much clear fluid and several thick flakes of fibrin were found in the pleuræ. The lungs were col-

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* Galvagni, Sopra un caso di mesenterite in uno saturnino, Riv. Clin., 1884, iii, 23.

lapsed. The pericardium was filled with fluid blood. It was somewhat thickened and the surface slightly rough. Smears of serous membranes showed red blood corpuscles, some lymphocytes, and large phagocytes. No bacteria were found. Hyperemia and edema of subcutaneous fat.

17. Guinea-pig 35 had a slight chronic pericarditis and a marked ascites and hydrothorax, without marked change in peritoneum or pleura, except a slight chronic perihepatitis. Marked general anasarca.

18. No lesions in serous membranes.

19. Guinea-pig 14 had a beginning chronic pericarditis only.

20. Guinea-pig 24*a* had about 10 c.c. of clear fluid with small flakes of fibrin in the peritoneum. There was present a marked irregular thickening of the parietal and visceral peritoneum, including the capsules of liver and spleen. The pericardium contained some slightly hemorrhagic fluid. It was covered with fibrin, and there were some recent adhesions. Much hemorrhagic fluid and much fibrin were found in both pleuræ. Both lungs were collapsed.

21. Guinea-pig 54 had marked ascites. The liver was covered with thin, easily detached shreds of fibrin. Both pleuræ were filled with clear fluid. The lungs were collapsed. Few drops of blood filled the pericardium. Very marked general anasarca.

22. Guinea-pig 33 had few drops of clear fluid in peritoneum. In several parts of the upper peritoneal cavity, especially on the surface of the liver, one noticed thin, non-adherent fibrinous deposits. The peritoneum was also slightly thickened all over. Both pleuræ were filled with clear liquid and the lungs were collapsed. The pericardium contained few drops of pure blood.

23. Guinea-pig 34 had few drops of fluid in peritoneum. The visceral pericardium was slightly thickened.

24. Guinea-pig 31 had little fluid in the serous cavities and a slight pericarditis.

25. Guinea-pig 32 showed but a slight pericarditis.

All three of these animals (Nos. 23, 24, 25) were extremely emaciated females, whereas the strong, well-nourished animals, more especially the males, were the ones which showed the marked lesions in the serous membranes.

26. Guinea-pig 46 had 30 c.c. of slightly bloody fluid in the peritoneum. The peritoneum, especially in the upper part of the abdominal cavity, was moderately thickened. Recent fibrinous deposits were found over the stomach and liver. Thick fibrous bands developed between stomach and mesentery, which had caused a partial strangulation of the small bowel. The duodenum was also surrounded by the adhesions. The stomach above the obstruction was greatly distended. The spleen was attached to the fundus of the stomach and the liver to the diaphragm. The pleuræ were covered with fibrin and contained little fluid. Few drops of bloody

fluid were found in the pericardium. In this case the diseased liver had been invaded by colon bacilli, which had caused extensive bacterial necrosis.

27. Guinea-pig 69 showed nothing but a slight pericarditis.

28. Guinea-pig 12 had a marked ascites, much fluid in both pleuræ, and some fluid in the pericardium. Both the parietal and visceral pericardium were slightly thickened.

The lesions in the serous membranes are evidently closely connected with the lead anemia. As a result of this condition the capillaries become more permeable, not only in the serous membranes, but all through the bodies of the animals, as is shown by the quite common occurrence of a general edema (Experiments 16, 17, 21). In all animals except those which were extremely emaciated the tissues were found not only hyperemic, but distinctly moist. It is possible that the hydremic condition of the blood itself contributes to the liability to leakage from the bloodvessels.

The character of the fluid which exudes into the serous cavities varies greatly, but it is always more or less hemorrhagic and has a tendency to coagulate on the serous surfaces, forming false membranes, which are later organized and lead to thickenings and adhesions. Fig. 7 shows a marked thickening of the capsule of the liver, produced in this way. In Fig. 10 similar capsular thickenings are represented in their gross appearance. In some of the cases the capsular thickening of the liver was so diffuse and well marked that the appearances of a "Zuckergussleber" were closely reproduced.

The danger of adhesions from this source is well shown in Case 26, in which a strangulation of the upper part of the small bowel had resulted from them.

In the pericardium almost pure blood was found quite commonly, and it is interesting to note that this blood was often unusually rich in nucleated reds, and sometimes contained large megaloblasts.

The effusions undoubtedly have somewhat of an inflammatory character, as evidenced by their tendency to coagulation and by the presence in them of rather large numbers of lymphocytes, and occasionally even polymorphonuclear leukocytes. Several specimens were carefully examined for bacteria in smears and culture, but none were found except in the case in which a bacterial infection had been caused as a result of the strangulation.

How far similar conditions occur in human cases of chronic lead-poisoning is still unknown. I have already referred to Galvagni's* case. In our series of 25 painters, pericarditis occurred only twice, both in cases of advanced chronic lead-poisoning. One of the cases showed a typical lead palsy, and both had lead anemia and severe progressive nephritis, marked arteriosclerosis, and some cardiac hypertrophy. In the one case (VIII, 34) the pericardium contained about 200 c.c. of a dark-red fluid with large, red, soft flakes of fibrin. It was covered with a moderately thick layer of grayish-red fibrin, which was firmly attached to the pericardium. No bacteria were found in a culture taken from the pericardium. Peritoneum and pleuræ were normal.

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* Galvagni, loc. cit.

In the other case (V, 50) about one tablespoon of slightly bloody fluid was found in the peritoneum. The pericardium contained about one-half teaspoonful of slightly turbid fluid. Both layers of the pericardium were covered with a thin layer of fibrin which could be detached easily. In the pleuræ over a liter of fluid was found on both sides, the fluid on the left side being slightly hemorrhagic. Unfortunately no bacteriological examination was made of the serous cavities in this last case.

In spite of the slight indications at the present time of a clinical significance of these experimental findings it may very well be that more careful attention directed to the possibility of such occurrences will reveal them much more commonly than would appear at the present time, and the diagnosis of chronic lead-poisoning may clear up some of those puzzling cases of polyserositis or polyorrhomenitis which have been described in literature, especially by Italian clinicians, and may contribute to the proper understanding of such conditions as Pick's pseudocirrhosis and Curschmann's "Zuckergussleber."

Conclusions. 1. Chronic lead-poisoning in guinea-pigs produces severe degenerative changes in the epithelium of the kidneys and of the liver, leading to necrosis. These destructive lesions are partly compensated for by constant regeneration.

2. In the kidneys these lesions may eventually cause collapse of certain groups of tubules associated with moderate proliferation of the connective tissue and some chronic inflammatory changes. The glomeruli in these foci usually show a fibrous thickening of the capsule. In exceptional instances the defects produced in this way are large enough to cause a somewhat granular gross appearance of the organs.

3. In the liver large areas of collapse occur much more frequently, so much so that marked irregularity of the surface resembling that observed in human cirrhosis is quite common. The connective-tissue proliferation associated with this process is extremely limited. The condition, therefore, cannot well be classified as a cirrhosis, but should be designated as a chronic focal atrophy.

4. Chronic lead-poisoning in guinea-pigs produces general increased permeability of the bloodvessels leading to the production of effusions, usually of a hemorrhagic character, into the serous cavities. These are most commonly observed in the pericardium, but the pleuræ and the peritoneum are often also involved in the process. False membranes are apt to form on the surface of the serous membranes, and their organization leads to the development

of the picture of a chronic polyserositis with fibrous thickening and sometimes adhesions. If this condition is more especially localized in the pericardium there may be the appearances of a pericarditic pseudocirrhosis; if more in the capsule of the liver, that of a "Zuckergussleber" may be reproduced.

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APPENDICITIS AS A SEQUELA OF TONSILLITIS.

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The occurrence of appendicitis as a sequela of tonsillitis has received less attention from clinicians in America and Great Britain than its practical importance warrants. Most of the standard works on medicine and surgery make no reference to it, and it is seldom noticed in current medical literature. This is the more remarkable, since the importance of the tonsil as the port of entry of many forms of systemic infection, and as the starting-point of disease in distant organs, has been well established in recent years in numerous contributions by recognized authorities. In this connection one need only enumerate general sepsis, acute rheumatism, chorea, endocarditis, pneumonia, pleurisy, empyema, meningitis, nephritis, urethritis, orchitis, thyroiditis, and cholecystitis, all of which have been definitely traced to acute tonsillar infections.

About a year ago a patient entered my service in St. Michael's Hospital, a young woman, who developed an abscess in the upper lobe of the right lung a week after an operation for removal of the tonsils during the subsidence of an acute angina.

The relationship between acute rheumatism and appendicitis has